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3-(4-Phosphoryl-4-methyl-2-oxopentyl)-3-hydroxyindolin-2-ones, the first phosphorus analogues of natural convolutamydines

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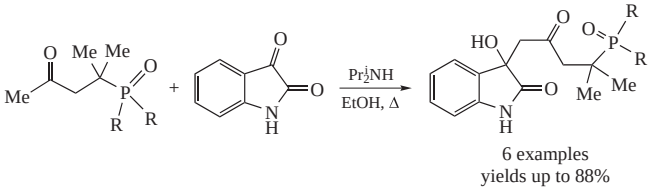
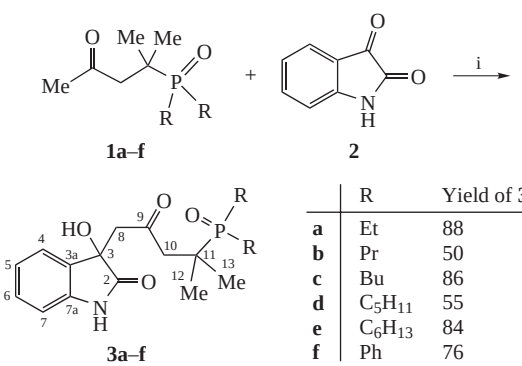
The first examples of phosphorus-containing analogues of natural alkaloids, convolutamydines, have been obtained by aldol condensation of 4-[dialkyl(diphenyl)phosphoryl]-4-methylpentan-2-one with isatin. An unusually facile reversible process of dehydration–hydration of these phosphorus-containing hydroxy indoles has been discovered.



Isatin derivatives show a broad spectrum of biological activity, *e.g.*, antimicrobial, antitumor, anti-HIV ones.[1–3] Furthermore, the high reactivity of carbonyl group at 3-position and benzo moiety are important factors determining the broad application of isatins in organic synthesis.[4–10] We have found previously that conjugation of isoniazid, an anti-tuberculosis agent, with dimephosphon [dimethyl (2-methyl-4-oxopent-2-yl)phosphonate], a known antiacidotic and metabolic agent,[11] or with its P–C analogues, dialkyl(2-methyl-4-oxopent-2-yl)phosphine oxides,[12] considerably reduces the toxicity of the conjugates without decreasing the pharmaceutical effect of isoniazid.[13,14] Here we report a synthesis of the first representatives of organophosphorus analogues of natural alkaloids, convolutamydines. It is known that the use of a catalytic amounts of a base in the reaction of isatin with aliphatic and fatty-aromatic ketones does not cause opening of the isatin ring driving the process towards cross-aldol condensation between the activated carbonyl group of isatin (the carbonyl component) and a methyl (methylene) group of a ketone (the methylene component). The products of these reactions are convolutamydine analogues possessing a broad range of biological activity.[15–18]

In this study, we have found that 4-[dialkyl(diphenyl)phosphoryl]-4-methylpentan-2-ones **1a–f** can undergo aldol condensation with isatin **2** to give phosphorus-containing analogues of convolutamydines **3a–f** (Scheme 1).† The reaction proceeds in refluxing ethanol in the presence of catalytic amounts (2–3 drops) of diisopropylamine.



	R	Yield of **3** (%)
a	Et	88
b	Pr	50
c	Bu	86
d	C_5H_{11}	55
e	C_6H_{13}	84
f	Ph	76

Scheme 1 *Reagents and conditions:* i, Pr$^i_2$NH, EtOH, 78 °C, 12–24 h.

It should be noted that despite the presence of two reactive sites (methyl and methylene groups) in phosphoryl ketones **1**, the reaction occurs exclusively at the methyl group, apparently due to steric factors. In the ^{1}H NMR spectra of 3-hydroxyindolin-2-ones **3**, the signals of the H^8 and H^{10} methylene protons are most characteristic. The H^8 protons are diastereotopic due to the effect of a chiral centre in the molecule and resonate as two related doublets 3.01 ppm (d, H^{8A}, J_{AB} 15.9 Hz) and 3.17 ppm (d, H^{8B}, J_{BA} 15.9 Hz). The H^{10} methylene protons appear as a strongly broadened doublet 2.57 ppm (d, $^3J_{PH}$ 8.1 Hz). The chemical shifts and multiplicity of the other aliphatic protons are, in general, similar to those for analogous phosphine oxides reported previously.[12] The IR spectra of compounds **3** are characterized by absorption bands corresponding to the C=O groups of the ketone (1710–1715 cm^{-1}) and amide (~1720 cm^{-1}) moieties. The structure of diethylphosphoryl representative **3a** was confirmed by X-ray diffraction (Figure 1).‡

† *3-[4-Dialkyl(diphenyl)phosphoryl-4-methyl-2-oxopentyl]-3-hydroxyindolin-2-ones* (*typical procedure*). A mixture of isatin (0.147 g, 1.0 mmol), phosphoryl ketone **1a–f** (1.0 mmol, for their synthesis see ref. 12) and a few drops of Pr$^i_2$NH in EtOH (5 ml) was stirred at 78 °C for 12–24 h. The reaction progress was monitored by TLC (EtOAc as an eluent, phosphine oxide **1** as a standard). After appropriate time (see Online Supplementary Materials), a solvent was rotary evaporated. The residue was purified by dry column flash chromatography (KSKG silica gel < 0.063 mm, eluent EtOAc for starting compounds and impurities, and ethanol for products).

‡ *Crystal data for* **3a**·2$CHCl_3$. $C_{20}H_{28}Cl_6NO_4P$, M = 590.10, monoclinic, space group $P2_1/n$, a = 14.963(12), b = 10.812(8) and c = 17.689(14) Å, β = 96.715(15)°, V = 2842(4) Å^3, Z = 4, d_{calc} = 1.379 g cm^{-3}. Total of 13456 reflections were measured on a Bruker Smart Apex II CCD diffractometer using graphite monochromated MoKα radiation at 293(2) K. Absorption corrections based on the Laue symmetry using equivalent reflections were applied, μ = 0.686 mm^{-1}. The structure was solved by direct methods using SHELXT[19] and refined by full-matrix least-squares on F^2 using SHELXL[20] with 5084 unique reflections, R_{int} = 0.1531. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were inserted at the calculated positions and refined as riding atoms. The disorder of a chloroform molecule